

- PART I. STUDIES OF THE SYNTHESIS OF BICYCLO[2.2.0]HEXANE AND CERTAIN REACTIONS OF 3-BENZHYDRILCYCLOPENTENE-4-CARBOXYLIC ACID
- PART II. ATTEMPTED SYNTHESSES OF BENZCYCLOBUTENE-3,4-DIONE AND BENZCYCLOBUTENE

by

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This work is dedicated to my parents, Mr. and Mrs. Albert J. Kovelesky, for their patience, encouragement and financial assistance which made this work possible.

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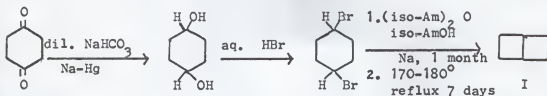
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PART I

STUDIES OF THE SYNTHESIS OF BICYCLO [2.2.0] HEXANE AND CERTAIN REACTIONS OF
3-BENZHYDRYLCYCLOPENTENE-4-CARBOXYLIC ACID

INTRODUCTION

The first synthesis of bicyclo [2.2.0] hexane (I) was reported⁴⁷ in 1927 by the general sequence of reactions illustrated. The reduction



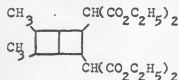
of cyclohexane-1,4-dione gave a mixture of cis- and trans-quinitol, which when treated with aqueous hydrobromic acid gave a mixture of cis- and trans-1,4-dibromocyclohexane. The two isomers were separated and it was reported that the cis- isomer led to bicyclo [2.2.0] hexane. Reported physical constants were b.p. 78.5-79.5° (732 mm), $n_D^{19} = 1.4475$, $d_4^{19} = .8245$.

Recently, a synthesis of bicyclo [2.2.0] hexane has been reported⁸ by the photolysis of bicyclo [3.2.0] heptan-3-one. The synthesis of this bicyclic



ketone involved a classical sequence of reactions some of which were previously described.¹ Reported physical constants were b.p. 90° (estimated), molecular weight 82 (by mass spectrometry), and vapor pressure at 26.5° was 100 mm.

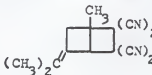
Cawley, Evans and Farmer⁷ reported on the synthesis of 5,6-dimethyl-2,3-bis (ethoxycarbonyl) methylbicyclo [2.2.0] hexane (II), which has not been repeated as yet. The bridged bicyclo [2.2.0] hexenone (III), which seems



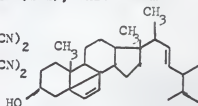
II



III



IV



V

unlikely in the light of its violation of Bredt's Rule, was reported by Mayuranathan and Guha.²⁶ A substituted bicyclo [2.2.0] hexane (IV) was reported⁴⁴ in connection with certain cyano-carbon chemistry. Dauben and Fonken⁹ have reported that ultraviolet irradiation of isopyrocalciferol produces the photoisomer (V) by cyclization of the cyclohexa-1,3-diene. Bring to the bicyclo [2.2.0] hexa-2-ene system.

OBJECTIVES OF THIS INVESTIGATION

The objectives of this investigation are:

1. To investigate the synthetic routes to bicyclo[2.2.0]hexane and certain derivatives.
2. To study the conjugate elimination reaction of 3-benz-hydrylcyclopentene-4-carboxylic acid.

DISCUSSION OF EXPERIMENTAL RESULTS

Proposed Route to Bicyclo [2.2.0] hexane

A rational approach to bicyclo [2.2.0] hexane (I) could conceivably start from bicyclo [3.2.0] hept-2-en-6-one or the Δ^3 -isomer which have been reported in the literature.^{4,6} The proposed route is illustrated in Fig. 1. The preparation of bicyclo [3.2.0] hept-2-ene was reported⁴

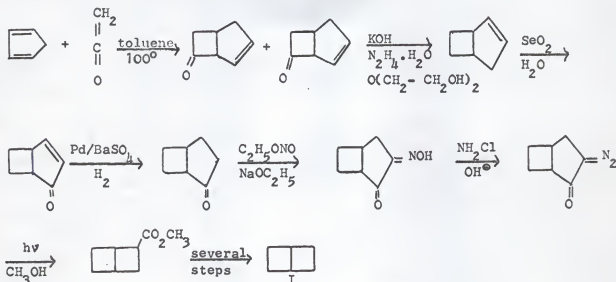


Fig. 1 Proposed Route to Bicyclo [2.2.0] hexane

in 70% yield by using the Huang-Minlon modification²⁰ of the Wolff-Kishner reduction. The technique of ultraviolet irradiation was adopted from similar work reported by Horner and co-workers,^{18,19} and Meinwald and his co-workers.^{27,28} This conversion appears to be quite general and should prove applicable to a synthesis of I.

Smith and co-workers³⁷ reported that ketene was found to be inert toward cyclopentadiene under any of the conditions tried. The first preparation of bicyclo [3.2.0] hept-2-en-6-one along with the Δ^3 -isomer was reported⁶ by heating a solution of ketene and cyclopentadiene in toluene under pressure in a steel cylinder at about 100° for one hour. The ketone, presumably resulting from a 1,2-addition of ketene to the diene, was indicated as having either structure VI or VII.



VI



VII

The crude ketone was purified through the sodium bisulfite addition compound which was cleaved with sodium carbonate.

Bloomquist and Kwiatek⁴ reported essentially the same reaction in 17-18% yield (as the semicarbazone based on ketene). The position of the double bond in VI and VII was not established. The crude ketone was purified through the semicarbazone derivative which was then cleaved with phthalic anhydride. The preparation of this ketone by the above method was reported by other workers who purified the crude ketone either through the semicarbazone derivative followed by cleavage with oxalic acid^{3b} or through the sodium bisulfite adduct.¹¹

The cycloaddition of ketene to cyclopentadiene as reported in the literature gave erratic yields. The best yield obtained by distillation of the crude ketone, purification via the semicarbazone derivative and subsequent cleavage of this derivative with pyruvic acid¹⁶ was 4.2% (based on ketene). A 2:1 molar ratio of cyclopentadiene to ketene was also tried without success. The preparation of bicyclo [3.2.0] hept-2-ene was accomplished in 55.3% yield which was lower than reported in the literature presumably due to impure starting bicyclic ketone.

Aliphatic as well as cyclic olefins are oxidized with selenium dioxide at the α -methylene position to yield α,β -unsaturated alcohols and ketones. The solvent may affect the nature of the end products of the reaction or influence the yield. For example, 1-methylcyclohexene in ethanol⁴⁶ leads to a mixture of 1-methylcyclohexen-6-ol (35%) and 1-methylcyclohexen-6-one (27%). When water was used as the solvent, a 90% yield of 1-methylcyclohexen-6-one resulted; whereas in acetic acid, a 40% yield of 1-methylcyclohexen-6-ol acetate resulted.

The oxidation of bicyclo [3.2.0] hept-2-ene was accomplished with selenium dioxide in aqueous solution and also in benzene. In both cases a mixture of alcohol and ketone was formed as indicated by their infrared spectrum. When water was used as the solvent, the ketone was the major product; whereas with benzene, the alcohol was the major product.

The mixture of alcohol and ketone could not be separated by distillation or semicarbazone formation of the bicyclic ketone.

The preparation of bicyclo [3.2.0] hept-2-en-4-ol of unassigned configuration was reported by Winstein and Stafford.⁴³ The infrared spectrum of this alcohol displayed strong bands at 12.7μ and 13.6μ which disappeared on hydrogenation. Both of these bands were present in the reaction product of bicyclo [3.2.0] hept-2-ene with selenium dioxide in aqueous solution or in benzene. The synthesis of bicyclo [3.2.0] hept-2-en-4-one has not been reported according to the literature.

The above alcohol-ketone mixture was subjected to several oxidizing agents in an attempt to convert it completely to bicyclo [3.2.0] hept-2-en-4-one. The use of chromium trioxide-acetic acid²² resulted in the formation of an α, β -unsaturated acid as indicated by the infrared spectrum of the reaction product. With manganese dioxide¹⁵ little or no reaction took place as indicated by comparison of the infrared spectrum of the reaction product with the starting mixture from the reaction of bicyclo [3.2.0] hept-2-ene with selenium dioxide in benzene. Chromium trioxide-pyridine³² seemed to be the most successful as the infrared spectrum of the reaction product indicated the presence of a carbonyl band (5.75μ) and the absence of a hydroxyl band. According to Bellamy³, α, β -unsaturated carbonyl groups in five-membered rings absorb at 1716 cm^{-1} (5.83μ). The amount of material used for the oxidations was too small, thus the pure bicyclo [3.2.0] hept-2-en-4-one could not be isolated.

The preparation of bicyclo [3.2.0] hept-2-en-6-one was not very successful, therefore the cycloaddition of diphenylketene to cyclopentadiene was substituted as the starting material in the above proposed route due to the reported ease of preparation in greater yield. Staudinger and co-workers^{39,41} first reported the cycloaddition of diphenylketene to cyclopentadiene and three structures were proposed for the product VIII, IX, X.



VIII



IX



X

From Staudinger's earlier work, structure X was eliminated but the position of the double bond (VIII or IX) was not established. Lewis and co-workers²³ have shown that the condensation product of diphenylketene and cyclopentadiene has structure VIII by degradation of this ketone to two isomeric α - and β -4,4'-diphenylbutane-1,2,3-tricarboxylic acids. These acids were prepared synthetically by the hydrolysis of the condensation product of bromodiphenylmethane and methyl sodio-propane- $\alpha,\alpha,\beta,\gamma$ -tetracarboxylate. Farmer and Farooq¹³ have reported degradations with Staudinger's adduct from cyclopentadiene and diphenylketene. Smith and co-workers³⁷ have described a degradation sequence for the diphenylketene-cyclopentadiene adduct by cleavage of the addition product followed by oxidation of the cleavage product.

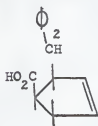
The cycloaddition of diphenylketene³⁰ to cyclopentadiene was carried out according to the method of Smith and co-workers³⁷ in 75-88% yield. The reduction of this ketone to 7,7-diphenylbicyclo [3.2.0] hept-2-ene was attempted by five methods. Clemmensen reduction²⁵, thioacetal formation⁴⁵ with subsequent Raney nickel cleavage²⁹, and the formation of the semicarbazone derivative with subsequent reduction of this semicarbazone as reported for the 7,7-dimethylbicyclo [3.2.0] hept-2-en-6-one case¹⁰ were not successful as only starting ketone was isolated from these reactions.

The fourth method consisted of lithium aluminum hydride reduction³⁵ of the starting ketone forming an alcohol of structure (XI), and conversion of this alcohol to the corresponding p-toluenesulfonate⁴² which were successful.

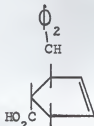


Attempted lithium aluminum hydride cleavage of this ester³³ resulted in the isolation of starting p-toluenesulfonate. The failure of this cleavage of the ester, presumably due to steric hinderance and its method of synthesis seemed to indicate that the alcohol probably has the endo-configuration, structure (XI).

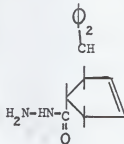
The fifth method consisted of a modified Wolff-Kishner reduction. A very interesting result was observed from this reaction in that diphenylmethane (29.6% yield) was identified as one of the reaction products along with a mixture of cis- and trans-3-benzhydrylcyclopentene-4-carboxylic acids (XII and XIII) and a trace quantity of 4-hydrazocarbonyl-3-benzhydrylcyclopentene (XIV).



XII



XIII



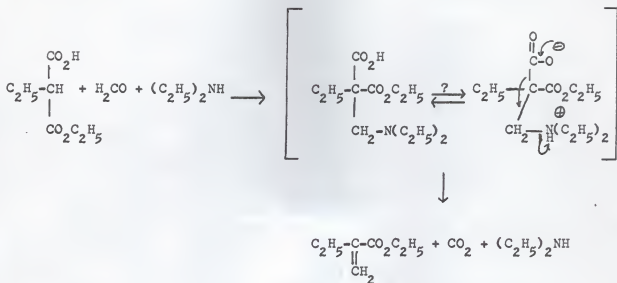
XIV

The initial cleavage of 7,7-diphenylbicyclo [3.2.0] hept-2-en-6-one results in the formation of the cis acid (XII). Under the reaction conditions the cis acid is isomerized to the more thermodynamically stable trans form which is the main acid isolated from the reaction.

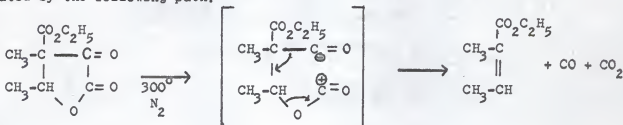
The identification of XIV was facilitated by an analysis which showed a molecular formula of $C_{19}H_{20}N_2O$, by the n.m.r. spectrum⁴⁸ which showed three exchangeable protons, and also by the infrared spectrum. Two independent syntheses of XIV were also accomplished: by refluxing 7,7-diphenylbicyclo [3.2.0] hept-2-en-6-one with hydrazine hydrate for eighteen hours, and by addition of the acid chloride of 3-benzhydrylcyclopentene-4-carboxylic acid in chloroform to excess hydrazine hydrate in an ice bath.

Elimination Studies of 3-Benzhydrylcyclopentene-4-carboxylic Acid

Few examples of a conjugate elimination appear in the literature but the examples are not well-defined. Mannich and Ritsert²⁴ reported that a monosubstituted malonic acid ester reacted with formaldehyde and diethylamine to form a nitrogeous condensation product. This product decomposed with the formation of carbon dioxide, diethylamine (as a condensation product with formaldehyde) and an α -substituted acrylic ester, so that the reaction course may be formulated by the following path:

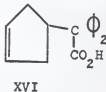
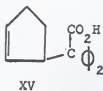


Hinder and co-workers¹⁷ reported that thermal decomposition of α -keto- θ , γ -dimethyl- θ -carboxyethyl- γ -valerolactone yielded 90% of the α -methyl ethyl crotonate. The reaction course may involve a conjugate elimination if postulated by the following path:



Schinz and Rossi³⁶ reported that thermolysis of α -keto- γ -isopropyl- θ -carboxyethyl- γ -valerolactone yielded θ -substituted ethyl acrylate. The theoretical equally possible α -formyl- θ -isopropyl ethyl acrylate was not detected so that the reaction can possibly be formulated like the above example.

Staudinger and co-workers^{40,41} first proposed that the reaction of VIII or IX with alcoholic sodium hydroxide resulted in cleavage to an acid of structure (XV or XVI).



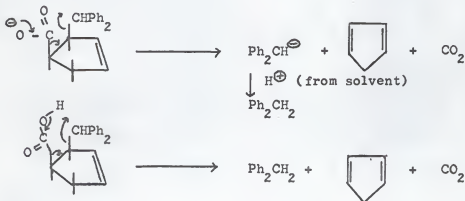
The cleavage was proposed this way in analogy from the results obtained from the diphenylketene-styrene adduct. However, as already pointed out, later workers^{13,23,37} reported that the reaction resulted in cleavage to two isomeric acids XII and XIII.

The hydrolytic fission of 7,7-diphenylbicyclo [3.2.0] hept-2-en-6-one was carried out according to the method of Smith and co-workers³⁷ in 80-85% yield. The conjugate elimination of diphenylmethane from 3-benzhydrylcyclopentene-4-carboxylic acid was studied under various reaction conditions and temperatures. The results are given in the following table.

Table 1. Thermolysis of 3-Benzhydrylcyclopentene-4-carboxylic Acid

Gm. Starting Acid	Solvent	Reaction Time	Temperature	Gm. (Yield) $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{C}_6\text{H}_5$	Gm. Recovered Acid
4.5	Ethylene Glycol	2 days	180°	0.1 (3.7%)	4.0
4.2	Diethylene Glycol	29 hrs.	200-250°	0.1 (3.9%)	4.1
1.7	Diethylene Glycol	8 hrs.	250°	0.2 (19.5%)	1.5
5.4	Diethylene Glycol	8 hrs.	280-300°	0.2 (6.1%)	5.2
3.1	Cu + Quinoline	18 hrs.	230°	- - -	2.8
5.1 as Na salt	None	45 min.	295-325°	1.2 (42.0%)	- -
4.7 as Na salt	Diethylene Glycol	9 1/2 hrs.	200-250°	0.2 (7.6%)	2.0

A very small quantity of diphenylmethane was isolated in each case under the reaction conditions. The following two mechanisms are proposed for the conjugate elimination of diphenylmethane from 3-benzhydrylcyclopentene-4-carboxylic acid.



The first mechanism involves the anion of the cis acid which is present to a very small extent in the reaction medium; whereas the second involves a six-membered ring transition state of the cis acid.

The pyrolysis of the sodium salt of 3-benzhydrylcyclopentene-4-carboxylic acid results in decomposition to form the stable entity, diphenylmethane.

SUMMARY

The cycloaddition of ketene to cyclopentadiene as reported in the literature gave erratic yields of bicyclo [3.2.0] hept-2-en-6-one along with the Δ^3 -isomer. This ketone mixture was successfully converted to bicyclo [3.2.0] -hept-2-ene using the Huang-Minlon modification of the Wolff-Kishner reduction. Allylic oxidation of bicyclo [3.2.0] hept-2-ene with selenium dioxide was carried out in aqueous solution and also in benzene. In both reactions a mixture of an alcohol and ketone resulted which could not be separated by distillation or by semicarbazone formation of the bicyclic ketone. Several oxidizing agents, for example, chromium trioxide-acetic acid, manganese dioxide, and chromium trioxide-pyridine complex, were tried in order to convert this mixture to bicyclo [3.2.0] hept-2-en-4-one. The use of chromium trioxide-pyridine complex seemed to give the best result as the infrared spectrum of the reaction product showed the presence of a carbonyl band and the absence of a hydroxyl band. Since a small quantity of material was used for the oxidation, the pure bicyclo [3.2.0] hept-2-en-4-one could not be isolated.

The preparation of bicyclo [3.2.0] hept-2-en-6-one was not very successful, thus the cycloaddition of diphenylketene to cyclopentadiene was considered as a starting material due to the fact that larger quantities of 7,7-diphenylbicyclo [3.2.0] hept-2-en-6-one could be obtained. The attempted Clemmensen reduction, thioacetal formation and semicarbazone formation resulted in the isolation of starting 7,7-diphenylbicyclo [3.2.0] hept-2-en-6-one. Lithium aluminum hydride reduction of 7,7-diphenylbicyclo [3.2.0] -hept-2-en-6-one resulted in the formation of an alcohol. This alcohol upon treatment with p-toluenesulfonyl chloride formed the corresponding p-toluenesulfonate. Attempted lithium aluminum hydride cleavage of this ester resulted in the isolation of starting p-toluenesulfonate. The fifth method consisted of a modified Wolff-Kishner reduction. A very interesting result was observed from this reaction in that diphenylmethane was identified as one of the reaction products along with a mixture of cis and trans-3-benzhydrylcyclopentene-4-carboxylic acids and a trace quantity of 4-hydrozocarbonyl-3-benzhydrylcyclopentene which was synthesized independently.

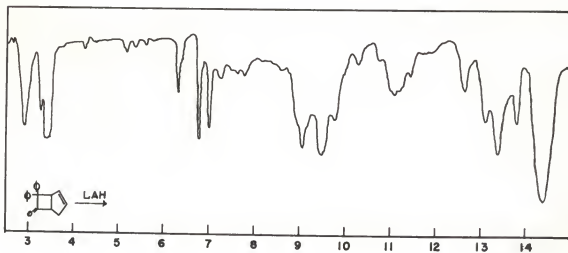
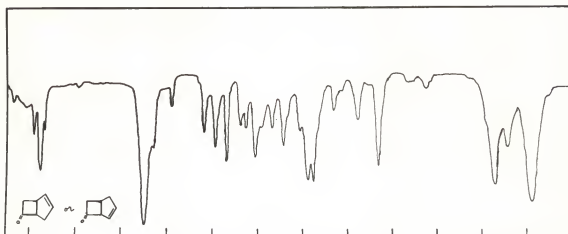
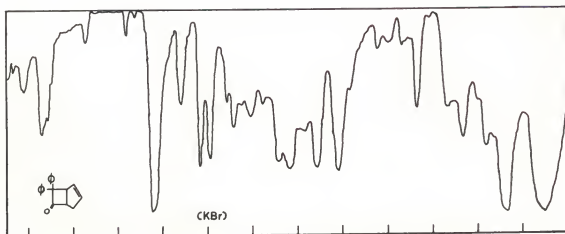
The conjugate elimination of diphenylmethane from 3-benzhydrylcyclopentene-4-carboxylic acid was studied under various reaction conditions. A very small quantity of diphenylmethane was isolated in each case. Two mechanisms are proposed to account for the conjugate elimination of diphenylmethane.

INFRARED SPECTRA

Bicyclo[3.2.0]hept-2-en-6-one (neat liquid)

7,7-Diphenylbicyclo[3.2.0]hept-2-en-6-one (KBr pellet)

Product from the Lithium Aluminum Hydride Reduction of 7,7-Diphenyl-
bicyclo[3.2.0]hept-2-en-6-one (neat liquid)

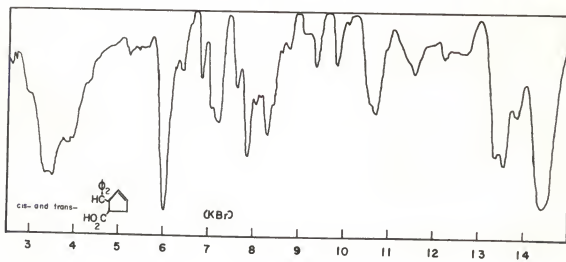
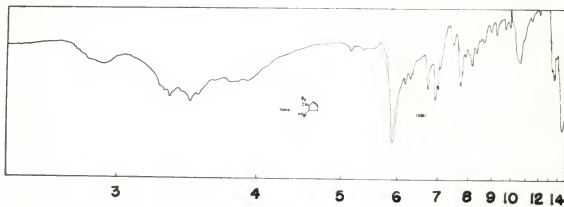
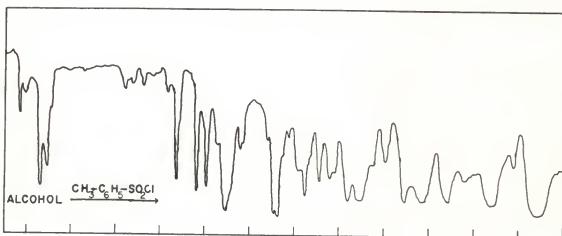


INFRARED SPECTRA

Product from the Treatment of 7,7-Diphenylbicyclo [3.2.0] hept-2-en-6-one
with Lithium Aluminum Hydride Followed by Treatment with p-Toluene-
sulfonyl Chloride (neat liquid)

trans-3-Benzhydrylcyclopentene-4-carboxylic Acid (KBr pellet)

cis- and trans-3-Benzhydrylcyclopentene-4-carboxylic Acid (KBr pellet)



EXPERIMENTAL⁴⁹

Cyclopentadiene. Cyclopentadiene was prepared by slowly distilling dicyclopentadiene, having a pot temperature about 200°, through a short glass-packed column. The product, which distilled at 39-41°, was collected in an ice-cooled receiver and was stored in a refrigerator for no more than one week until used.

Ketene. The pyrolysis was carried out by refluxing diketene or acetone over a metal filament heated to a dull redness. A modification of the Ott³¹ ketene lamp was found satisfactory. The ketene lamp consisted of a 200 ml. flask surmounted by a pyrolysis chamber of glass in which was suspended a filament of 24 gauge Chromel A wire; the glass frame on which the wire was mounted was sealed to a ground-glass stopper so that the filament could be removed easily. The pyrolysis chamber was fitted at the top with a reflux condenser leading into a cold trap cooled by a solid carbon dioxide-isopropyl alcohol bath. The depolymerization of diketene was the best method for the preparation of ketene as a lower temperature was required for the pyrolysis and the rate of conversion to ketene was much higher than by the use of acetone.

Bicyclo [2.2.0] hept-2-en-6-one. This ketone was prepared according to the method of Blomquist and Kwiatek^h with the following modifications. A sealed tube was used instead of a steel lecture bottle as the reaction vessel, a 2:1 molar ratio of cyclopentadiene to ketene was tried without success, and the cleavage of the semicarbazone derivative was accomplished with pyruvic acid.¹⁶ A sealed tube was weighed empty and then ketene was distilled into the sealed tube cooled by a dry ice-isopropyl alcohol bath and the tube was reweighed. A mixture of toluene and cyclopentadiene, cooled by a dry ice-isopropyl alcohol bath, was added to the sealed tube. The sealed tube was heated at 100° for two hours and then cooled to room temperature. The reaction mixtures from several runs were combined and on distillation the crude ketone, b.p. 145-150°, was obtained. The results from four such procedures are illustrated in the following table.

Table 2. Preparation of Bicyclo [3.2.0] hept-2-en-6-one

Run	: Sealed Tube Runs	: Moles : Ketene	: Moles : Cyclopentadiene	: Ml. : Toluene	: Gms. : Crude Ketone	: % Yield : Crude Ketone
I	7	1.10	1.62	116	36.3	30.5
II	21	4.60	4.98	353	73.6	14.8
III	5	2.56	2.62	189	56.4	20.3
IV	7	2.90	5.61	350	0	0

Impure ketone from Run III was purified through its semicarbazone. From 56.4g. of crude ketone, there was obtained 39.7g. (9.4% based on ketene) of semicarbazone. The derivative was recrystallized from methanol-water (3:1).

The cleavage of the semicarbazone was accomplished utilizing pyruvic acid¹⁶ in the reversal. A typical reaction: a solution of 18g. (.109 mole) of the above semicarbazone in 150 ml. of glacial acetic acid warmed to 110° to which was added a solution consisting of 16g. of anhydrous sodium acetate and 38.4g. of a 50% by weight solution of aqueous pyruvic acid in 50 ml. of hot acetic acid. The second flask was rinsed with an additional 10 ml. portion of glacial acetic acid which was added to the reaction flask. After heating the reaction at 105-110° for twenty-five minutes, 150 ml. of water was added dropwise over a period of one hour. The solution was cooled to room temperature and diluted with an additional 500 ml. of water. The solution was extracted with three 150 ml. portions of diethyl ether. The ether solution was washed in turn with two 75 ml. portions of 10% sodium hydroxide and two 50 ml. portions of water, and dried over magnesium sulfate. After the solvent was removed on a steam cone, the residual ketone was distilled in vacuo affording 10g. (85%) of bicyclo [3.2.0] hept-2-en-6-one, b.p. 55-62° (18 mm), $n_D^{20} = 1.4771$ [reported^h b.p. 62-63.5° (20 mm), yield 84.9%, $n_D^{20} = 1.4819$]. Other runs gave yields of 54%, 55%, and 44.3%. The infrared spectrum of this ketone, given on page 15, compares with the one reported in the literature.¹²

Bicyclo [3.2.0] hept-2-ene. This olefinic hydrocarbon was prepared according to the method of Blomquist and Kwiatak^h using the Huang-Minlon modification²⁰ of the Wolff-Kishner reduction, b.p. 97-104°, yield 55.3%, $n_D^{21} = 1.4605$ [reported^h b.p. 101.5-103°, yield 70%, ($n_D^{20} = 1.4623$)¹²]. The infrared spectrum of this olefinic hydrocarbon compared favorably with the one reported in the literature.¹²

Oxidation of Bicyclo [3.2.0] hept-2-ene.

1. With Selenium Dioxide in Water. In a 100 ml. three-necked flask, equipped with a magnetic stirrer, a dropping funnel, and a reflux condenser, were placed 50 ml. of water and 5.3g. (.0478 mole) of sublimed selenium dioxide. The mixture was heated to 50-55° and stirred until the solid went into solution. Then 4.5g. (.0478 mole) of bicyclo [3.2.0] hept-2-ene was added in one lot and the resulting mixture was refluxed with continued stirring for six hours. The solution turned red as the mixture started to reflux. The precipitated selenium was filtered from the hot solution. The solution was cooled, extracted with diethyl ether and dried over magnesium sulfate. The solution was then diluted with skelly B.

Removal of traces of colloidal selenium from the reaction mixture was accomplished by chromatography on a column of alumina provided with a layer of commercial precipitated silver.¹⁴ The above diethyl ether-skelly B solution was passed through this column and the resulting solution was dried. Evaporation of the solvent yielded a dark brown oil. The infrared spectrum of this oil showed a weak hydroxyl band (2.8μ) and an intense carbonyl band (5.7μ). On attempted distillation of this brown oil, a black tar resulted.

2. With Selenium Dioxide in Benzene. In a 100 ml. three-necked flask, equipped with a magnetic stirrer, a dropping funnel and a reflux condenser, were placed 2.4g. (.0213 mole) of freshly sublimed selenium dioxide and 25 ml. of benzene. The mixture was heated to 50-55° with stirring. Then 2.0g. (.0213 mole) of bicyclo [3.2.0] hept-2-ene was added in one lot and the resulting mixture was refluxed with continued stirring for ten hours. The precipitated selenium was filtered from the hot solution, the solution allowed to cool and dried over magnesium sulfate. The solution was then diluted with diethyl ether.

A chromatography column using a 1:1 ratio of freshly precipitated silver metal¹⁴ and neutral aluminum oxide was prepared for the removal of traces of colloidal selenium from the reaction mixture. The diethyl ether-benzene solution was passed through this column and the resulting solution was dried. Evaporation of the solvent yielded a brown liquid. The infrared spectrum of this liquid showed a hydroxyl band (2.95μ) and a carbonyl band (5.6μ). The hydroxyl band in this spectrum was more intense than in the previous method.

Attempted Oxidation of the Reaction Product of Bicyclo [3.2.0] hept-2-ene with Selenium Dioxide in Benzene.

1. With Chromium Trioxide-Acetic Acid. In a 50 ml. round-bottomed flask was placed 2.0g. of the reaction product of bicyclo [3.2.0] hept-2-ene with selenium dioxide in benzene. Ten ml. of acetic acid was added and the solution was warmed slightly to dissolve the mixture. Then 3.0g. (.030 mole) of chromium trioxide was added to the warm solution and a vigorous reaction took place which had to be cooled in an ice bath. After the reaction subsided, the solution was warmed on a steam cone for three hours. The solution was cooled, filtered, and extracted with diethyl ether. The ether solution was washed in turn with sodium bicarbonate and water, and was dried over magnesium sulfate. Evaporation of the solvent yielded a brown liquid. The infrared spectrum of this liquid showed a carbonyl band (5.9 μ), characteristic of an α,β -unsaturated acid.

2. With Manganese Dioxide. The manganese dioxide was prepared according to the method of Attenburrow and co-workers² starting with manganese sulfate monohydrate. A solution of 2.8g. of the reaction product of bicyclo [3.2.0] hept-2-ene with selenium dioxide in benzene dissolved in 100 ml. of skelly B (b.p. 40-46°) was stirred with the above manganese dioxide, 38.8g. (.447 mole) for 24 hours. The solution was filtered and the solvent was evaporated to yield a yellow liquid. The infrared spectrum of this liquid showed a hydroxyl band (2.95 μ) and a carbonyl band (5.8 μ). The intensity of the carbonyl band did not vary as compared to the starting material thus indicating that very little or no reaction took place.

3. With Chromium Trioxide-Pyridine. The chromium trioxide-pyridine complex was prepared according to the method of Poos and co-workers.³² The general procedure which was found to be safe and reproducible involved the addition of chromium trioxide to pyridine. If pyridine was added to chromium trioxide, the mixture usually inflamed. To 83.5 ml. (1.04 mole) of reagent grade pyridine at 15-20° was added 8.64g. (.0864 mole) of chromium trioxide in portions with swirling. After about one-third of the chromium trioxide was added and mostly dissolved, the yellow complex began to precipitate. At the end, a slurry of the complex in pyridine remained.

A solution of 2.8g. of the reaction product of bicyclo [3.2.0] hept-2-ene with selenium dioxide in benzene dissolved in 83.5 ml. of pyridine was added dropwise to the above chromium trioxide-pyridine complex. The reaction flask was stoppered, the contents were mixed thoroughly and allowed to stand at room temperature overnight. The reaction mixture was poured into ice water, extracted with three 25 ml. portions of diethyl ether. The combined ether extracts were washed with water and dried over magnesium sulfate. Evaporation of the solvent yielded an oil which showed a carbonyl band (5.75 μ) and the absence of a hydroxyl band.

Benzil Monohydrazone. This monohydrazone of benzil was prepared according to the method of Smith and Hoehn³⁸, m.p. 149-151°, yield 96.4% [reported³⁸ m.p. 149-151°, yield almost quantitative].

Diphenylketene. This ketene was prepared according to the method of Nenitzescu and Solomonica³⁰ by the oxidation of benzil monohydrazone, b.p. 90-110° (.5mm), yield 42.7-60.7% [reported³⁰ b.p. 119-121° (3.5mm), yield 64%].

7,7-Diphenylbicyclo [3.2.0] hept-2-en-6-one. This ketone was prepared according to the method of Smith and co-workers³⁷ by the cycloaddition of diphenylketene to cyclopentadiene, m.p. 86-88°, yield 75-88% [reported³⁷ m.p. 88-89°, yield 92%].

Attempted Reductions of 7,7-Diphenylbicyclo [3.2.0] hept-2-en-6-one.

1. Clemmensen Method. Amalgamated zinc was prepared by shaking for five minutes a mixture of 8.5g. (.13 moles) of mossy zinc, .86g. mercuric chloride, 14.3 ml. of water, and .43 ml of concentrated hydrochloric acid contained in a 200 ml. round-bottomed flask. The solution was decanted and the following reagents are added, in order named, to the zinc: 5.4 ml. of water, 12.5 ml. of concentrated hydrochloric acid, 10 ml. of toluene and 5.0g. (.0192 moles) of 7,7-diphenylbicyclo [3.2.0] hept-2-en-6-one. The flask was fitted with a reflux condenser and the reaction mixture was boiled vigorously for thirty hours. Three 3.5 ml. portions of concentrated hydrochloric acid were added at approximately six hour intervals during the refluxing period.

After cooling the reaction to room temperature, the two layers were separated. The aqueous layer was diluted with 100 ml. of water and extracted with two 50 ml. portions of diethyl ether. The toluene layer and ether extracts were combined, washed with water and dried over calcium chloride. The solvent was removed by distillation to yield an oil. This oil was identified as starting ketone by its infrared spectrum.

2. Attempted Semicarbazone Formation.

A. 7,7-Diphenylbicyclo [3.2.0] hept-2-en-6-one, 1.0g. (.0038 mole), was dissolved in 10 ml. of ethanol. Water was added until the solution was faintly turbid and the turbidity was removed with a few drops of ethanol. Then 1.0g. of semicarbazide hydrochloride and 1.5g. of sodium acetate were added. The mixture was vigorously shaken, and the Erlenmeyer flask was placed in a beaker of boiling water and allowed to cool. The flask was placed in a refrigerator and a white solid resulted. This solid, 1.0g., was identified as starting ketone by its infrared spectrum.

B. A mixture of 2.1g. (.0081 moles) of 7,7-diphenylbicyclo [3.2.0] -hept-2-en-6-one, 2.1g. semicarbazide hydrochloride and 3.15g. of sodium acetate was refluxed in a solution of 25 ml. ethanol and 10 ml. of water for eighteen hours. After cooling the reaction to room temperature, a solid was filtered off. Upon continued evaporation of the solvent, 2.1g. of a white solid resulted. This solid was a mixture of semicarbazide and starting ketone. Upon repeated crystallization from dilute ethanol, 1.5g. of starting ketone was obtained as identified by its infrared spectrum.

3. Attempted Thioacetal Formation. 7,7-Diphenylbicyclo [3.2.0] hept-2-en-6-one, 2.5g. (.00963 mole), was added slowly with cooling (ice-bath) to a mixture of 10 ml. (.135 mole) of ethyl mercaptan, .25g. of freshly fused zinc chloride and .2g. of anhydrous sodium sulfate contained in 100 ml. round-bottomed stoppered flask. The mixture was maintained at 0-5° for twenty hours and then at room temperature for four hours, whereupon it was poured into 10 ml. of ice and water in a separatory funnel. The water insoluble layer was washed consecutively with 10% aqueous sodium hydroxide and water and dried with sodium sulfate. The infrared spectrum of the resulting liquid was identical with that of starting ketone.

4. Lithium Aluminum Hydride Reduction of 7,7-Diphenylbicyclo [3.2.0] -hept-2-en-6-one XI. 7,7-Diphenylbicyclo [3.2.0] hept-2-en-6-one, 7.0g. (.0269 mole), in 50 ml. of dry tetrahydrofuran was added dropwise to a stirred suspension of .9g. (.0238 mole) of lithium aluminum hydride in 50 ml. of dry tetrahydrofuran. After the addition was complete, the mixture was refluxed for three and one-half hours.

Sufficient 10% sulfuric acid was added slowly with stirring to dissolve the solid and the solution was extracted with diethyl ether and dried over calcium chloride. The product was distilled at 110-115° (1-.2 mm) to yield 4.0g. (57%) of a viscous liquid. The infrared spectrum of this liquid indicated that reduction to the alcohol had taken place, OH band (2.95 μ) and C-O stretching (9.06 μ) for a secondary alcohol.

Preparation of the p-Toluenesulfonate of 7,7-Diphenylbicyclo [3.2.0] - hept-2-en-6-ol. The above alcohol, 4.0g. (.0153 mole), was dissolved in 40 ml. of dry pyridine and the solution was cooled to -5° in an ice-salt bath. p-Toluenesulfonyl chloride, 3.22g. (.01683 mole), was added in one portion, the flask was stoppered and the suspension was gently swirled by hand with cooling in an ice-salt mixture until all the tosyl chloride had dissolved. After standing at 0° overnight, the solution was poured into 200 ml. of ice and water with swirling and cooling. The aqueous pyridine solution was extracted with three 50 ml. portions of chloroform and the combined chloroform extracts washed successively with ice-cold dilute sulfuric acid, water, and sodium bicarbonate solution. The chloroform solution was dried with sodium sulfate and the solvent was evaporated to dryness under reduced pressure to yield a brown oil. The infrared spectrum of this oil indicated the formation of the p-toluenesulfonate, the SO₂-O- bands (7.48 μ) and (8.65 μ).

Attempted Lithium Aluminum Hydride Cleavage of the above p-Toluenesulfonate. To 1.0g. (.0263 mole) of lithium aluminum hydride in 50 ml. of dried tetrahydrofuran was added a solution of 6.36g. (.0153 mole) of the crude p-toluenesulfonate dissolved in 50ml. of dry tetrahydrofuran in an ice bath. After the addition was complete, the mixture was heated under reflux with stirring for three hours. The mixture was cooled in an ice bath and water was added to decompose the excess lithium aluminum hydride. The solution was filtered and then extracted with two 50 ml. portions of diethyl ether. The ether extracts were washed with dilute sulfuric acid and water, and dried over magnesium sulfate. Evaporation of the solvent yielded an orange liquid. The infrared spectrum of this liquid was identified as starting p-toluenesulfonate.

5. Modified Wolff-Kishner Reduction. To a solution of sodium, 4.90g. (.211 mole), in 200 ml. of diethylene glycol was added 18.3g. (.0704 mole)

of 7,7-diphenylbicyclo [3.2.0] hept-2-en-6-one and 21 ml. of hydrazine hydrate. The mixture was refluxed for ten hours. After cooling the reaction to room temperature, the reaction mixture was diluted with water and extracted with diethyl ether. The combined ether extracts were dried and the solvent was removed to yield 3.5g. (29.6%) of diphenylmethane and .4g. (2.0%) of 4-hydrazocarbonyl-3-benzhydrylcyclopentene. These two compounds were separated with skelly B. The diphenylmethane was identified by its infrared and n.m.r. spectra and its b.p. $131-3^{\circ}$ (15 mm) [reported²¹ 141° (27 mm)] .

The 4-hydrazocarbonyl-3-benzhydrylcyclopentene was recrystallized from dilute ethanol, was sublimed at $127-133^{\circ}/.1$ mm. and melted at $159-160^{\circ}$. The n.m.r. spectrum⁴⁸ indicated 20 protons with three labile hydrogens as determined by D_2O equilibration. The infrared spectrum showed a secondary amide band (2.88μ), a free amino group (3.0μ) and an amide carbonyl band (6.1μ).

Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.08%; H, 6.85%; N, 9.59%

Found: C, 78.31%; H, 7.19%; N, 9.70%

The above aqueous layer was acidified with dilute hydrochloric acid and the solution was extracted with diethyl ether. The ether extracts were dried and the solvent was evaporated to yield 12g. (61.4%) of a white solid, m.p. $125-7^{\circ}$ [reported¹³ m.p. $125-7^{\circ}$]. This solid was identified by its infrared spectrum given on page 17 and melting point to be a mixture of cis- and trans-3-benzhydrylcyclopentene-4-carboxylic acids. Partial separation of these two isomeric acids was accomplished with skelly B, and then recrystallization with dilute methanol yielded an acid melting at $148-9^{\circ}$ [reported¹³ m.p. $148-9^{\circ}$]. The infrared spectrum of this trans acid is given on page 17.

4-Hydrazocarbonyl-3-benzhydrylcyclopentene

1. By Refluxing Hydrazine Hydrate with 7,7-Diphenylbicyclo [3.2.0] -hept-2-en-6-one. 7,7-Diphenylbicyclo [3.2.0] hept-2-en-6-one, 3.6g. (.0138 mole), was added to 25 ml. of 85% hydrazine hydrate and the solution was refluxed for eighteen hours. After cooling the reaction to room temperature, the solution was poured into water and extracted with diethyl ether. The combined ether extracts were washed with water and dried over magnesium sulfate. Upon evaporation of the solvent, 3.4g. (86%) of 4-hydrazocarbonyl-3-benzhydrylcyclopentene resulted.

After recrystallization from dilute ethanol and sublimation at $129-131^{0.05}$ mm., the solid melted at $157-159^{\circ}$. The infrared spectrum compared with the one obtained from the modified Wolff-Kishner reduction.

2. By Addition of the Acid Chloride of 3-Benzhydrylcyclopentene-4-carboxylic Acid to Hydrazine Hydrate. 3-Benzhydrylcyclopentene-4-carboxylic acid, 2.3g. (.0083 mole), was mixed with thionyl chloride, 1.48g. (.0124 mole). The solution was stirred at room temperature for three hours and then warmed on a steam bath for an hour. The excess thionyl chloride was removed by heating the reaction on a steam cone under water aspirator pressure. After standing for twelve hours, the acid chloride solidified. The infrared spectrum of this acid chloride was taken.

The acid chloride was dissolved in 50 ml. of chloroform and was slowly added to 8.27g. (.165 moles) of hydrazine hydrate cooled in an ice bath over a period of one hour. The solution was stirred while warming up to room temperature. The two layers were separated and the aqueous layer was extracted with chloroform. The combined chloroform extracts were dried over sodium sulfate. Upon evaporation of the solvent, 2.1g. (87%) of a 4-hydrazocarbonyl-3-benzhydrylcyclopentene resulted. After recrystallization from dilute ethanol and sublimation at $127-130^{0.01-.02}$ mm., the solid melted at $157-159^{\circ}$. The infrared spectrum was identical with the one obtained from the modified Wolff-Kishner reduction.

3-Benzhydrylcyclopentene-4-carboxylic Acid. This acid was prepared according to the method of Farmer and Farooq¹³ by the hydrolytic fission of 7,7-diphenylbicyclo [3.2.0] hept-2-en-6-one, m.p. $125-7^{\circ}$, yield 81-89% [reported¹³ m.p. $125-7^{\circ}$].

Elimination Studies of 3-Benzhydrylcyclopentene-4-carboxylic Acid. The general procedure was to add 3-benzhydrylcyclopentene-4-carboxylic acid and a base in a solvent and this mixture was heated at a certain temperature for a period of time, a sealed tube was generally used as the reaction vessel. After cooling the reaction to room temperature, the solution was diluted with water. The resulting basic solution was extracted with diethyl ether and dried over magnesium sulfate. Evaporation of the solvent yielded diphenylmethane as identified by comparison of its infrared spectrum with the Sadtler Tables.

The above basic solution was then acidified with dilute hydrochloric acid, extracted with diethyl ether and dried over magnesium sulfate. Evaporation of the solvent yielded 3-benzhydrylcyclopentene-4-carboxylic acid as identified by its infrared spectrum.

The results of the elimination studies of 3-benzhydrylcyclopentene-4-carboxylic acid are given in the following table.

Table 3. Thermolysis of 3-Benzhydrylcyclopentene-4-carboxylic Acid

Gm. Starting Acid	Solvent	Reaction Time	Temper- ature	Gm. $\text{C}_6\text{H}_5\text{CH}_2$ (Yield)	Gm. Recovered Acid
4.5	Ethylene Glycol	2 days	180°	0.1(3.7%)	4.0
4.2	Diethylene Glycol	29 hrs.	200-250°	0.1(3.9%)	4.1
1.7	Diethylene Glycol	8 hrs.	250°	0.2(19.5%)	1.5
5.4	Diethylene Glycol	8 hrs.	280-300°	0.2(6.1%)	5.2
3.1	Cu + Quinoline	18 hrs.	230°	- - -	2.8
5.1 as Na Salt	None	45 min.	295-320°	1.2(42.0%)	- -
4.7 as Na Salt	Diethylene Glycol	9 1/2 hrs.	200-250°	0.2(7.6%)	2.0

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48. The author wishes to express his appreciation to Dr. Donald P. Hollis, Varian Associates for determination of the n.m.r. on the A-60 spectrophotometer.
49. All melting points were taken on a Kofler hot stage which was calibrated. The boiling points are uncorrected. The infrared spectra were taken on a Perkin-Elmer model 137 double beam recording spectrophotometer unless otherwise stated. Elementary analyses were performed by Galbraith Laboratories, Inc.

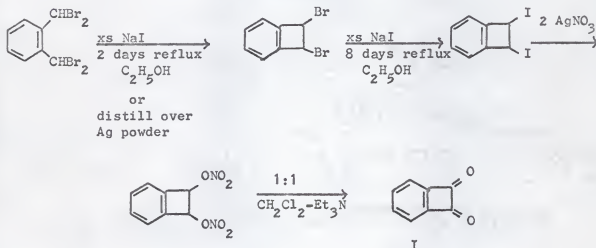
PART II

ATTEMPTED SYNTHESSES OF BENZCYCLOBUTENE-3,4-DIONE AND BENZCYCLOBUTENE

INTRODUCTION

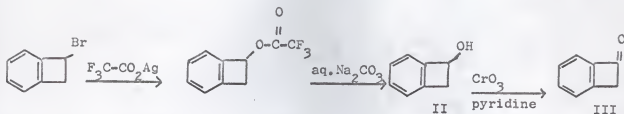
The chemistry of small-ring compounds has been the object of considerable interest and research among organic chemists in recent years. Vogel⁴⁶ has recently reviewed this enlarging area of chemistry. Of particular significance to the present investigation is the work directed toward the synthesis of benzcyclobutene and related derivatives.

The first synthesis of benzcyclobutene-3,4-dione (I) was carried out by Cava and Napier^{13,14,15} by the general sequence of reactions illustrated.

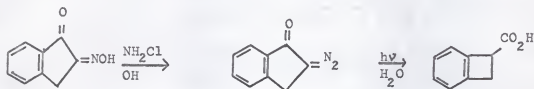


The mechanism for the formation of 1,2-dibromobenzocyclobutene with iodide ion has been shown to involve a o-quinodimethane⁸ by trapping the intermediate in the reaction as a Diels-Alder adduct with N-phenylmaleimide or maleic anhydride. The 1,2-diiodobenzocyclobutene when treated with two equivalents of silver nitrate gave a mixture of cis- and trans- dinitrates. Either isomer when refluxed one hour with 1:1 methylene chloride-triethylamine gave the resulting benzcyclobutene-3,4-dione.

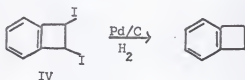
The synthesis of 1,2-dicarbomethoxymethylenebenzocyclobutene and 1-keto-2-carbomethoxymethylenebenzocyclobutene was achieved by the reaction of benzcyclobutene-3,4-dione with triphenylphosphinecarbomethylenebenzocyclobutene.¹⁷ The synthesis of benzocyclobutenol (II) and benzocyclobutenone (III) was reported¹² by the sequence of reactions shown.



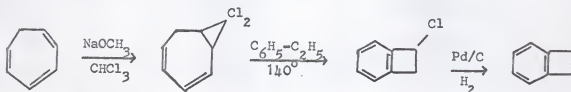
A novel synthesis of 1-keto-3,4,5,6-tetramethylbenzocyclobutene was reported.³⁰ The photolysis of α -diazoindanone was reported^{10,32} to form benzocyclobutene-1-carboxylic acid by the sequence of reactions shown.



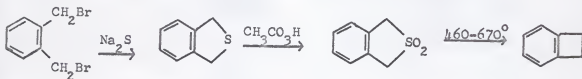
The synthesis of the parent hydrocarbon, benzocyclobutene, has been reported by four routes: the reaction of $\alpha, \alpha', \alpha'', \alpha'''$ -tetrabromo-*o*-xylene with sodium iodide^{13,14,16,23,25} followed by reduction of the diiodide (IV),



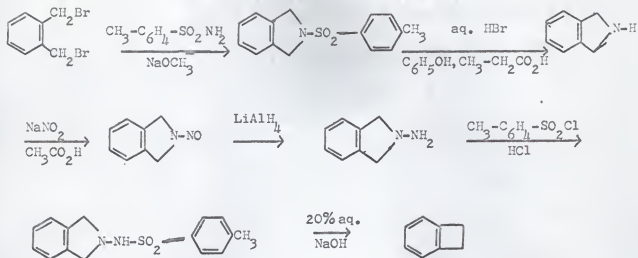
a synthesis starting with cycloheptatriene,³



the pyrolysis of 1,3-dihydroisothianaphthene-2,2-dioxide⁷,



and a synthesis starting with α, α' -dibromo-*o*-xylene.²



Cava and co-workers have also reported the synthesis of naphtho [b] -cyclobutene¹⁸, benzo [1,2:4,5] dicyclobutene⁹, and the attempted synthesis of 1,2-diphenylbenzocyclobutene.¹¹

OBJECTIVES OF THIS INVESTIGATION

The objectives of this investigation are:

1. To investigate possible synthetic routes to benzcyclobutene-3,4-dione and related diones starting from the corresponding hydrazides.
2. To investigate possible synthetic routes to benzcyclobutene and related hydrocarbons via 1,4-dihydrophthalazines.

DISCUSSION OF EXPERIMENTAL RESULTS

The reaction route used to prepare benzcyclobutene-3,4-dione was laborious due to the fact that the mixture of dibromide and diiodide was very difficult to separate into its components, and few experimental details were given. The molecule was highly strained as indicated by the infrared data given by Cava and Napier.¹⁵ It would be interesting to see if benzcyclobutene-3,4-dione and related diones of the cyclobutane and cyclobutene system could be obtained by the following proposed route, illustrated for benzcyclobutene-3,4-dione, in Fig. 1.

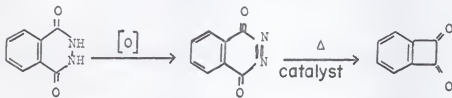
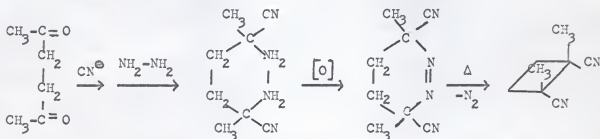


Fig. 1 Proposed Route to Benzcyclobutene-3,4-dione

The above sequence of reactions was reported in the case of open-chained hydrazides³⁴, for example, the preparation of diacetyl. Similar elimination of nitrogen from azo compounds was studied by Overberger^{40,41} in a series of twenty-five papers. A Strecker type synthesis route was used.



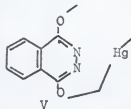
The starting 2,3-dihydropthalazine-1,4-dione, hereafter called phthalic hydrazide for brevity, was prepared according to the method of Drew and Hart.²⁰ Other methods have also been reported.^{24,41}

The corresponding 1,2,4,5-tetrahydropyridazine-3,6-dione, hereafter called succinic hydrazide for brevity, was prepared according to the method of Stefange and Howard.⁴⁵ Its preparation has also been reported by the reduction of maleic hydrazide.²²

The above methods seemed to be applicable as a general method for other cyclic as well as alkyl hydrazides.^{27,31,44}

The attempted oxidation of phthalic hydrazide was studied with various oxidizing agents. Various products were isolated from these oxidations; for example, phthalic acid, phthalic anhydride, phthalimide, N-aminophthalimide, or starting hydrazide. The formation of phthalic acid and phthalic anhydride indicated that nitrogen or hydrazine was eliminated from the hydrazide, but under the reaction conditions cyclization to the dione was not favored. The formation of phthalimide involved the loss of ammonia, whereas the formation of N-aminophthalimide involved rearrangement to the more stable five-membered ring. The expected benz- [d] -3,4,5,6-tetrahydro-3,6-diketopyridazine was in no case observed.

The thermal decomposition of phthalic hydrazide with yellow mercuric oxide at 230-250° formed phthalimide in 39% yield, free mercury and a grayish-white solid. This solid contained mercury, gave a positive nitrogen and may have a structure of this type:



A similar type structure was reported in the literature.³⁴ This solid when treated with iodine and refluxed in diethyl ether formed N-aminophthalimide. Upon treatment of this grayish-white solid with aqueous sodium hydroxide and refluxing for eighteen hours, a yellow solid which contained nitrogen was formed. Acidification of this solid seemed to form o-phthalaldehyde plus other unidentified material. The reaction of phthalic hydrazide with yellow mercuric oxide³⁸ in skelly B formed phthalimide as the only product.

The attempted oxidation of phthalic hydrazide with fuming nitric acid¹⁹ in concentrated nitric acid formed phthalimide in 10% yield and phthalic acid in 56.5% yield. The reaction of phthalic hydrazide with chloranil in refluxing xylene and the pyrolysis with sulfur gave no reaction as only starting hydrazide was isolated.

The attempted oxidation of phthalic hydrazide with N-bromosuccinimide⁴⁷ in tertiary butyl alcohol-water solvent with triethylamine formed four products.

These products were separated as various fractions and identified as succinimide, triethylamine hydrobromide, N-aminophthalimide and starting hydrazide. The reaction of phthalic hydrazide with lead tetra-acetate³³ in acetic acid formed phthalic anhydride in 14.6% yield and N-aminophthalimide in 8.4% yield.

The attempted oxidation of phthalic hydrazide with potassium permanganate⁴⁰ in acetone and also with alkaline calcium hypochlorite³⁷ in methanol resulted in the formation of N-aminophthalimide as the only product.

The attempted oxidation of succinic hydrazide was studied in two cases. The reaction with aqueous mercuric chloride³⁴ formed a grayish-white solid similar to V. This solid when treated with iodine³⁴ and refluxed in diethyl ether or heated with hydrochloric acid possibly formed N-aminosuccinimide. This solid was also refluxed for thirty minutes with 10% sodium hydroxide and the resulting solution was acidified to form succinic acid. The second reaction was the attempted oxidation of succinic hydrazide with potassium permanganate⁴⁰ in acetone. The product could possibly be N-aminosuccinimide.

By modifying the above reactions slightly, the parent hydrocarbons could also be obtained by the following proposed route, illustrated for benzcyclobutene, in Fig. 2. This sequence of reactions was reported for a similar type of open-chain as well as cyclic hydrazo compounds.^{36,40}

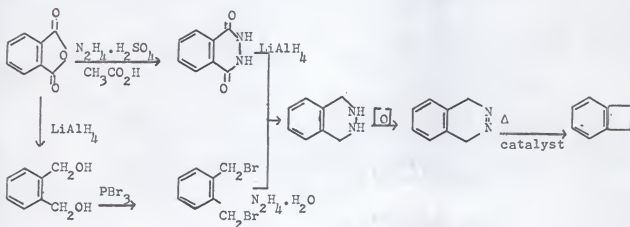


Fig. 2 Proposed Route to Benzcyclobutene

Two different methods were used in an attempt to prepare 1,2,3,4-tetrahydrophthalazine: the lithium aluminum hydride reduction of phthalic hydrazide, and the reaction of hydrazine hydrate with α,α' -dibromo-o-xylene. The synthesis of 1,2,3,4-tetrahydrophthalazine by reduction of the corresponding phthalazine was reported.²⁵ Two methods were reported for the synthesis of phthalazine.^{25,26}

The corresponding 1,2-dihydropyridazine-3,6-dione, hereafter called maleic hydrazide for brevity, was prepared according to the method of Harris and Schoene.²⁹ Other methods are also reported.^{1,21,24}

Maleic hydrazide was used instead of phthalic hydrazide but the reduction was not successful presumably due to the low solubility of the hydrazides in tetrahydrofuran. The hydrazides were not soluble in pyridine, diethyl ether, or acetonitrile which could have been used for the solvent. Hinman³¹ reported that acylhydrazines, which have hydrogens instead of methyl groups on the acyl-substituted nitrogens, are reduced much more slowly or not at all with lithium aluminum hydride in refluxing diethyl ether or tetrahydrofuran.

The second method attempted for the preparation of 1,2,3,4-tetrahydrophthalazine started with the reduction of phthalic anhydride with lithium aluminum hydride.³⁹ The preparation of α,α' -dibromo-o-xylene was carried out by using phosphorus tribromide with phthalyl alcohol. Other methods for the preparation of α,α' -dibromo-o-xylene were reported.^{4,5,42} The reaction of α,α' -dibromo-o-xylene with hydrazine hydrate was not successful as the expected 1,2,3,4-tetrahydrophthalazine was not formed.

SUMMARY

The formation of the starting hydrazides could be easily obtained and in fair yields as reported in the literature.

Various reagents and experimental conditions were tried in an effort to oxidize phthalic hydrazide to the corresponding cyclic azodiacyl compound. Various products were isolated from these oxidations, for example, phthalic acid, phthalic anhydride, phthalimide, N-aminophthalimide, or starting hydrazide. These products were identified by physical properties and by their infrared spectrum as reported in the literature. The expected benz [d] -3,4,5,6-tetrahydro-3,6-diketopyridazine was not formed in any case.

The attempted oxidation of succinic hydrazide was also unsuccessful as the corresponding 3,4,5,6-tetrahydro-3,6-diketopyridazine was not formed. The infrared spectrum of the reaction products seemed to indicate the formation of succinic acid and N-aminosuccinimide.

Two methods were attempted in an effort to prepare 1,2,3,4-tetrahydro-phthalazine: the lithium aluminum hydride reduction of phthalic hydrazide (maleic hydrazide was actually used) and the addition of hydrazine hydrate to α,α' -dibromo-o-xylene. Acylhydrazines, which have hydrogens instead of methyl groups on the acyl-substituted nitrogens, are reduced much more slowly or not at all with lithium aluminum hydride presumably due to the low solubility of the acylhydrazine in tetrahydrofuran. The second method was also unsuccessful as tars could only be isolated from the reaction.

EXPERIMENTAL⁴⁸

Phthalic Hydrazide. This hydrazide was prepared according to the method of Drew and Hart²⁰, m.p. 332-334°, yield 43% [reported²⁰ m.p. 334°, yield 60%].

Succinic Hydrazide. This hydrazide was prepared according to the method of Stefange and Howard⁴⁵, m.p. 264-268°, yield 55.3% [reported⁴⁵ m.p. 266-8°, yield 58%].

Maleic Hydrazide. This hydrazide was prepared according to the method of Harris and Schoene²⁹, m.p. 302-304°, yield 43.2% [reported²⁹ m.p. 305°, yield 87%].

Phthalyl Alcohol. This alcohol was prepared according to the method of Nystrom and Brown³⁹, m.p. 62-63°, yield 70.5% [reported³⁹ m.p. 64°, yield 87%].

α,α' -Dibromo-o-xylene. In a 500 ml. three-necked flask fitted with a reflux condenser, a stirrer, and a dropping funnel protected from air was placed 18.76g. (.136 mole) of phthalyl alcohol. Dried benzene, 250 ml., was added and the mixture was cooled in an ice bath. Then a solution of 13.3 ml. (.14 mole) of phosphorus tribromide in dried benzene was added dropwise over thirty minutes. The ice bath was removed and the solution was warmed to room temperature and stirred for one hour. Heat was then applied cautiously and the solution was refluxed for twenty hours. The solution was cooled to room temperature and poured onto ice and the product was extracted with chloroform. The organic phase was separated, washed in turn with dilute sodium bicarbonate and water, and dried over calcium chloride. The drying agent was removed and the solvent was evaporated in yield 24.44g. (68.2%) of α,α' -dibromo-o-xylene, m.p. 91-93° [reported⁴² m.p. 93°].

Attempted Reaction of α,α' -Dibromo-o-xylene with Hydrazine Hydrate. A mixture of 24.44g. (.0926 mole) of α,α' -dibromo-o-xylene, 100 ml. of 85% hydrazine hydrate, and 300 ml. of water was placed in a one liter flask and refluxed for sixteen hours. After cooling the solution to room temperature, it was filtered from a black resin and made basic with solid sodium hydroxide. The solution was extracted many times with diethyl ether, dried, and the solvent was evaporated to give a dark brown tar.

A picrate derivative of this material could not be prepared, thus indicating that the 1,2,3,4-tetrahydrophthalazine was not formed.

Attempted Lithium Aluminum Hydride Reduction of Maleic Hydrazide. Tetrahydrofuran (dried over lithium aluminum hydride) was distilled into a one liter three-necked flask equipped with a stirrer, and a reflux condenser. Powdered lithium aluminum hydride, 15.7g (.413 mole) was added followed by 10g (.0895 mole) of maleic hydrazide. The mixture was heated under reflux on a steam bath for six days. After cooling the reaction, it was placed in an ice bath. The intermediate reduction complex and the excess hydride were hydrolyzed with a calculated amount of water and 15% sodium hydroxide which produced a precipitate of aluminum hydroxide. The solid was filtered and washed with diethyl ether. The organic layer was separated from the aqueous layer and dried over anhydrous sodium sulfate. After evaporation of the solvent a brown solid resulted. This solid was recrystallized from 95% ethanol to form a white solid, which was dried and melted at 250-252°. The product seemed to be impure succinamide, reported²² m.p. 260°.

Anal. Calcd. for $C_4H_8N_2O_2$: C, 41.37%; H, 6.91%; N, 24.15%.

Found: C, 31.7%; H, 7.09%; N, 24.91%.

Reactions of Phthalic Hydrazide with Various Oxidizing Agents.

1. Thermal Decomposition with Mercuric Oxide. Phthalic hydrazide, 5.0g (.0308 mole), and 20g (.0092 mole) of mercuric oxide (yellow) were both dried in a vacuum oven at 80° and then mixed in a 50 ml. pear-shaped flask. The flask was immersed in a sand bath and the receiver in an ice bath. The flask was heated between 230-250° for fifteen minutes, then allowed to cool down to room temperature. The solid remaining in the flask was partly soluble in hot 95% ethanol; a grayish-white solid remained undissolved along with metallic mercury. The material, 1.7g, which dissolved in the hot alcohol, was isolated and identified as phthalimide by comparison of its infrared spectrum, melting point (m.p. 228-230° C) and mixed melting point with an authentic sample.

The grayish-white solid plus the metallic mercury weighed 20g. This grayish-white solid contained mercury and gave a positive nitrogen test. It was suspended in absolute diethyl ether and treated with 6.0g. of iodine with exclusion of moisture in the presence of .5g. of magnesium oxide.

The solution was refluxed on a steam cone for twenty hours. After cooling the reaction to room temperature, the solution was filtered, washed in turn with sodium thiosulfate and water, and dried over calcium chloride. Evaporation gave N-aminophthalimide as identified by comparison of its infrared spectrum with the literature.⁶

The grayish-white solid was also heated under reflux with aqueous sodium hydroxide for eighteen hours. After cooling the reaction to room temperature the solution was filtered to remove mercury and a yellow solid. This yellow solid was recrystallized from 95% ethanol, dried and melted at 230-236°. The solid burned and left a residue; also it gave a positive nitrogen test. This material was treated with hydrochloric acid and then heated. After cooling the solution, it was extracted with diethyl ether, dried and the solvent was evaporated to yield a white solid, m.p. 55-56°, which gave a negative nitrogen test. The infrared spectrum of this solid seemed to be a mixture of o-phthalaldehyde plus unidentified material.

2. Reaction with Mercuric Oxide in Skelly B. Phthalic hydrazide, 7.32g.(.0452 mole), 17.0g.(.0786 mole) of mercuric oxide (yellow) and 150 ml. of skelly B were placed in a pressure bottle. The bottle was stoppered, placed in a Parr hydrogenation apparatus and shaken mechanically at 50° for two days. After cooling the solution to room temperature, it was filtered. The skelly B was evaporated to give a reddish-orange oil. The infrared spectrum of this oil resembled phthalimide from an authentic sample.

3. Reaction with Nitric Acid. Phthalic hydrazide, 11.2g.(.069 mole), was added to a 200 ml. round-bottomed flask, then 45 ml. of fuming nitric acid and 30 ml. of concentrated nitric acid were cautiously added. The mixture was allowed to stand at room temperature for three days. The excess nitric acid was evaporated on a steam cone under water aspirator pressure and a white solid resulted. The white solid was recrystallized from dilute ethanol, dried and melted at 202-203°. This white solid was sublimed and two products were separated. The product that sublimed was phthalimide, 1.0g.(m.p. 228-230°C), whereas phthalic acid, 6.5g.(m.p. 208-210°C), remained behind. Both products were identified by comparison of their infrared spectra, melting points and mixed melting points with authentic samples.

4. Reaction with Chloranil in Xylene. A mixture of 2.42g. (.0149 mole) of phthalic hydrazide and 10.88g. (.0442 mole) of chloranil in 150 ml. of xylene was heated under reflux for eight hours. After cooling the reaction to room temperature, the solution was filtered and washed in turn with water, dilute sodium hydroxide and then water again. The xylene solution was dried over calcium chloride and the solvent was removed by distillation. The residue contained starting material as the only identifiable compound (2.0g).

5. Reaction with N-Bromosuccinimide. Phthalic hydrazide, 5.0g. (.034 mole), was added to a mixture of 25 ml. of tertiary butyl alcohol and 25 ml. of water contained in a 100 ml. round-bottomed flask fitted with a reflux condenser. The flask was placed in an ice bath and then 15.7 ml. (.102 mole) of triethylamine was added. N-Bromosuccinimide, 6.75g. (.068 mole), was added and the flask was swirled gently in the ice bath. The reaction was allowed to warm up to room temperature over a period of twelve hours. The solvent was evaporated on a steam cone under water aspirator pressure and the resulting solid was dried. The solid was extracted with a mixture of acetone and diethyl ether many times. After drying the solution and evaporation of the solvent, two fractions resulted. The first fraction was a white solid (.4g) which was identified as succinimide, and the second fraction after evaporation of the solvent was a yellow oil (.2g) which was identified as N-aminophthalimide.

After the initial extraction with acetone plus diethyl ether mixture, a solid remained undissolved. Upon addition of water to the solid, two fractions were separated and identified as the starting hydrazide and triethylamine hydrobromide. The identifications of all products were made by the comparison of their infrared spectrum with those of authentic samples.

6. Reaction with Lead Tetraacetate. To a solution of 5.0g. (.037 mole) of phthalic hydrazide in 50 ml. of acetic acid, contained in a one liter three-necked flask, was added a solution of 26.7g. (.060 mole) of lead tetraacetate dissolved in 200 ml. of methylene chloride during the course of twenty minutes. The reaction was maintained at 0 to 10° during the addition, then warmed to room temperature, and stirred for an additional fifteen minutes. A white precipitate of lead diacetate was formed.

Water (200 ml.) was added and the reaction mixture was stirred for two hours at room temperature. The mixture was filtered and the two layers were separated. The methylene chloride layer was washed in turn with water and dilute aqueous sodium bicarbonate, and was dried over sodium sulfate. Evaporation of the solvent yielded 1.3g. of a solid which contained two products. The products were separated by sublimation. Phthalic anhydride (.8g) was sublimed at $100^{\circ}/.005$ mm. whereas N-aminophthalimide (.5g) did not sublime at this temperature. The phthalic anhydride was identified by comparison of its infrared spectrum, melting point and mixed melting point with an authentic sample. The N-aminophthalimide was identified by comparison of its spectrum with the literature.⁶

7. Thermal Decomposition with Sulfur. Phthalic hydrazide, 5.0g.(.0308 mole), and 10g.(.312 mole) of sulfur were dried and then were mixed in a 50 ml. pair-shaped flask. The flask was immersed in a sand bath and heated between $200-250^{\circ}$ for twenty minutes. The reaction was cooled to room temperature and the remaining solid was partially dissolved in acetic acid. The solution was filtered hot to remove the excess sulfur and cooled to room temperature. Upon continued evaporation of the acetic acid, 4.8g. of starting material was obtained as identified by infrared.

8. Reaction with Potassium Permanganate. In a 500 ml. three-necked flask a solution of 5.0g.(.0308 mole) of phthalic hydrazide in 100 ml. of acetone was placed and then was cooled to 0° in an ice bath. A solution of 7.0g.(.0443 mole) of potassium permanganate dissolved in 250 ml. of acetone was slowly added to the above solution. After the potassium permanganate was added, the solution was stirred at room temperature for six hours. The acetone was evaporated and the solid remaining was taken up in diethyl ether. The ether solution was washed twice with sodium bisulfite, twice with water and then dried over magnesium sulfate. Evaporation of the solvent yielded N-aminophthalimide as identified by comparison of its infrared spectrum with the literature.⁶

9. Reaction with Calcium Hypochlorite. Phthalic hydrazide, 2.0g.(.0123 mole) was added to 50 ml. of methanol, and then 22 ml. of sodium hydroxide (.05M) was added. The solution was stirred with 5.54g.(.0338 mole) of calcium hypochlorite (72.3% available chlorine) for two hours.

The solution was poured into 150 ml. of ice water and then was extracted with chloroform. The chloroform solution was washed with saturated sodium chloride, dried over magnesium sulfate, and evaporated to form a semi-solid. This material was identified as N-aminophthalimide by comparison of its infrared spectrum with the literature.⁶

Reactions of Succinic Hydrazide with Various Oxidizing Agents.

1. Reaction with Mercuric Chloride and then Iodine. To 6.1g.(0.535 mole) of succinic hydrazide and 1.3g. of sodium in 50 ml. of methanol was added 14.2g. of mercuric chloride in 300 ml. of water. This solution was refluxed for one hour. After the solution was cooled to room temperature, a fine white precipitate of mercury compound resulted. The solution was centrifuged and the solid was washed with methanol, then diethyl ether, and was dried in a vacuum oven at 80°. The solid was suspended in absolute diethyl ether, treated with 11.0g. of iodine with exclusion of moisture in the presence of 1.0g. of magnesium oxide, and heated for two days on a steam cone. The solution was filtered, washed in turn with sodium thiosulfate and with water, and dried over magnesium sulfate. Evaporation of the solvent yielded a reddish-orange oil. This oil could possibly be N-aminosuccinimide as indicated by its infrared spectrum.

The above mercury compound was treated with dilute hydrochloric acid and refluxed for fifteen minutes. The solution was cooled to room temperature, extracted with diethyl ether and dried. Upon evaporation of the solvent, a solid resulted which may possibly be N-aminosuccinimide as indicated by its infrared spectrum.

The above mercury compound was also treated with 10% sodium hydroxide and refluxed for thirty minutes. Metallic mercury was formed and the solution was filtered. The solution was acidified, extracted using a continuous extractor with diethyl ether as the solvent, and dried. After evaporation of the solvent, a white solid (1.7g) resulted which was identified as succinic acid by comparison of its infrared spectrum and melting point with the literature.

2. Reaction with Potassium Permanganate. In a 500 ml. three-necked flask, a solution of 6.0g.(.0526 mole) of succinic hydrazide in 100 ml. of acetone was placed and was cooled to 0° in an ice bath.

A solution of 9.9g.(.0628 mole) of potassium permanganate dissolved in 200 ml. of acetone was slowly added to the above solution and the mixture was stirred at room temperature for ten hours. The solvent was evaporated and the solid remaining was taken up in diethyl ether. The ether solution was washed twice with sodium bisulfate, twice with water and then dried over magnesium sulfate. The solvent was evaporated to give a semi-solid which could possibly be N-aminosuccinimide as indicated by its infrared spectrum.

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48. All melting points taken in an oil bath and boiling points were uncorrected. The infrared spectra were taken on a Perkin-Elmer model 137 double beam recording spectrophotometer. Elementary analyses were performed by Galbraith Laboratories, Inc.

VITA

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PART I. STUDIES OF THE SYNTHESIS OF BICYCLO [2.2.0] HEXANE AND CERTAIN REACTIONS OF 3-BENZHYDRILCYCLOPENTENE-4-CARBOXYLIC ACID

PART II. ATTEMPTED SYNTHESSES OF BENZCYCLOBUTENE-3,4-DIONE AND BENZCYCLOBUTENE

by

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A logical starting point for a synthetic route to bicyclo [2.2.0] hexane appeared to be the cycloaddition of ketene to cyclopentadiene reported to give bicyclo [3.2.0] hept-2-en-6-one along with the Δ^3 -isomer. The reaction of ketene to cyclopentadiene gave erratic yields of bicyclo [3.2.0] hept-2-en-6-one along with the Δ^3 -isomer. This ketone mixture was successfully converted to bicyclo [3.2.0] hept-2-ene in 55% yield using the Huang-Minlon modification of the Wolff-Kishner reduction. Allylic oxidation of bicyclo [3.2.0] hept-2-ene with selenium dioxide was carried out in aqueous solution and also in benzene. In both reactions a mixture of alcohols and ketone was obtained which could not be separated by distillation or semicarbazone formation of the ketone.

Several oxidizing agents, for example, chromium trioxide-acetic acid, manganese dioxide, and chromium trioxide-pyridine, were tried in order to oxidize the above mixture completely to bicyclo [3.2.0] hept-2-en-4-one. The use of chromium trioxide-pyridine seemed to give the best result as the infrared spectrum of the reaction product showed the presence of a carbonyl band and the absence of hydroxyl band. Since only a small quantity of material was used for the oxidation, the pure bicyclo [3.2.0] hept-2-en-4-one was not isolated.

The preparation of bicyclo [3.2.0] hept-2-en-6-one was not very successful, thus the ready cycloaddition of diphenylketene to cyclopentadiene was carried out giving 7,7-diphenylbicyclo [3.2.0] hept-2-en-6-one in 75-88% yield. Reduction of this ketone to 7,7-diphenylbicyclo [3.2.0] hept-2-ene was attempted by five methods. The attempted Clemmensen reduction, semicarbazone formation with subsequent reduction, and thioacetal formation with subsequent Raney nickel cleavage were unsuccessful as only starting ketone was isolated. The fourth method consisted of three reactions: lithium aluminum hydride reduction to 7,7-diphenylbicyclo [3.2.0] hept-2-en-6-ol, conversion of this alcohol to the corresponding p-toluenesulfonate ester, and attempted lithium aluminum hydride cleavage of this p-toluenesulfonate resulted in isolation of starting ester.

The fifth method was a modified Wolff-Kishner reduction. An interesting result was observed from this reaction in that diphenylmethane was identified as one of the reaction products along with a mixture of cis- and trans-3-benzhydrylcyclopentene-4-carboxylic acid and a trace quantity of 4-hydrazocarbonyl-3-benzhydrylcyclopentene. Independent syntheses of the latter compound were accomplished.

The fact that diphenylmethane was observed prompted a study of the conjugate elimination of 3-benzhydrylcyclopentene-4-carboxylic acid. This acid was prepared in 81-89% yield by the alkaline cleavage of 7,7-diphenylbicyclo [3.2.0] hept-2-en-6-one. Various reaction conditions were tried to effect this conjugate elimination of diphenylmethane, but only a very small quantity was observed in each case. Two mechanisms were proposed for the elimination: the first involves the anion of the cis acid whereas the second involves a six-membered ring transition state of the cis acid.

The approach to benzcyclobutene-3,4-dione and benzcyclobutene used in this investigation was the elimination of nitrogen from certain diacylazo compounds. The formation of the starting hydrazides could be easily accomplished as reported in the literature. Various oxidants and experimental conditions were tried in an effort to oxidize phthalic hydrazide to the corresponding benz[d]-3,4,5,6-tetrahydro-3,6-diketopyridazine. Various products were isolated from these oxidations, for example, phthalic acid, phthalic anhydride, phthalimide, N-aminophthalimide or starting hydrazide. These products were identified by physical properties and by their infrared spectrum. The expected benz[d]-3,4,5,6-tetrahydro-3,6-diketopyridazine was not observed in any case.

The attempted oxidation of succinic hydrazide was also unsuccessful as the corresponding 3,4,5,6-tetrahydro-3,6-diketopyridazine was not observed. The infrared spectrum of the reaction products seemed to indicate the formation of succinic acid and N-aminosuccinimide.

Two methods were attempted in an effort to prepare 1,2,3,4-tetrahydro-phthalazine: the lithium aluminum hydride reduction of phthalic hydrazide (maleic hydrazide was actually used) and the addition of hydrazine hydrate to α,α' -dibromo-o-xylene. Both methods were unsuccessful.